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Applicant:	Prussak et al.	Art Unit:	1644
Serial No.:	10/006,305	Examiner:	Gambel, Phillip
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Title:	NOVEL CHIMERIC TNF LIGANDS		

DECLARATION OF DR. KENNETH A. FOON

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I, Dr. Kenneth A. Foon, declare as follows:

1. I am currently a Professor of Medicine at the University of Pittsburgh School of Medicine, as well as the Director of Clinical Investigations and the Hematologic Malignancy Program of the University of Pittsburgh's Cancer Institute. Previously, I served as the Director of Clinical Development for Oncology at Abgenix, Inc. and was a Clinical Professor of Medicine at Stanford University's School of Medicine. My other past positions have included Professor of Medicine and Director of the Barrett Cancer Center at the University of Cincinnati, Professor of Medicine and Director of the Markey Cancer Center at the University of Kentucky, Professor of Medicine and Director of the Division of Clinical Immunology at Roswell Park Cancer Institute, and Associate Member of the Scripps Research Institute and Clinical Director of the Green Cancer Center at the Scripps Hospital. Prior to that, I was a Senior Investigator at, and Head of, the Clinical Investigations Section of the Biological Response Modifiers Program

at the National Cancer Institute. I am also the author and co-author of more than 150 scientific publications and over 150 non-peer reviewed publications. I am currently the associate editor of Clinical Cancer Research and am on the editorial boards of both the Journal of Clinical Immunology and Journal of Biotherapy.

2. Because of their importance in the communication of immune cells, I am particularly interested in the therapeutic use of molecules that target the TNF family. Towards this end, I conducted the original clinical trials that used soluble TNF for solid tumor cancers and I continue to follow this field closely.

3. I have been asked to comment on the question of whether one of ordinary skill in the art would have had a reasonable expectation that a chimeric molecule including domain IV of TNFα (including a TNFα receptor binding site) and domain III of CD154, (lacking a metalloproteinase cleavage site) would substantially resist cleavage if expressed on a cell membrane. In particular, I was asked if such an expectation would be reasonable in view of the disclosures of a patent application (now US Patent No. 7,070,771, the "Kipps Application"), and a paper by Mueller, et al. (J. Biol. Chem. Vol. 274, No. 53, pp. 38112-38118). For background, I also reviewed the most recent Office Action in the above-referenced patent application dated.

4. From my review, the original Kipps' patent application provides an overview of the TNF family of biomolecules, including discussion of their structure, expression and catabolism. The published literature that was current in 1997 is reviewed. The application confirms the inventors' discovery of differential expression of the murine versus human CD154 molecule in human CD40+ cells. The discovery is the basis for a suggestion that domains can be swapped between the TNF family members (especially human/murine chimera) and that the resulting chimeric molecules could have desirable properties. In particular, it is suggested that such molecules containing murine-derived domains could be expressed in cells that would not otherwise express a particular TNF family member; e.g., CD40 ligand expression could be obtained in

CD40+ human cells. However, nothing in the application points to CD154/ TNFα as having properties different or more desirable than those possessed by any of the other potential chimeric constructs described. More particularly, the Kipps application does not point to CD154/TNFα chimera (with or without intact metalloproteinase cleavage sites) as being less susceptible to membrane cleavage than any other molecules.

5. The Mueller paper published in 1999 investigates the in vitro and in vivo biological activity of a "non-cleavable" transmembrane form of mouse TNF. To produce the non-cleavable molecule, the authors deleted all the known cleavage sites from the murine molecule. Using the L6 mutant TNF product, Mueller and coworkers demonstrated that this functional TNF molecule was expressed for the most part in a membrane stabilized manner. Although this molecule had enhanced stability, soluble TNF was still detectable in the cell supernatants from the L6 TNF transfected cells (Figure 2B, lane 5). It is of further interest that the relative cleavage of the soluble TNF molecule was cell line dependent as the soluble molecule was demonstrated in the cell supernatant from the murine NIH3T3 fibroblasts but not from the murine T cell hybridoma By155.16.

6. Therefore, the Mueller paper does not suggest that removing a metalloproteinase cleavage site from a TNF molecule will necessarily abrogate TNF cleavage. Further, nothing in the paper would cause one to suspect that removing a metalloproteinase cleavage site from the CD154 element of a TNFα chimera would produce even the same resistance to cleavage enjoyed by the TNF molecule tested by Mueller, much less greater resistance to cleavage. Given that the Mueller molecule was still cleaved to a substantial degree, an option more likely to have been pursued toward further stabilizing TNF would have been to continue to delete regions until a satisfactory result was achieved in the murine 3T3 cells.

7. In my opinion, on reading the Kipps application and the Mueller paper, it is at most possible that one might decide to try removing a metalloproteinase site from one or more of the chimeric "domain swap" constructs described in the application. However, the purpose of doing so would only have been to obtain molecules having murine elements (e.g., CD40 ligand) that could be expressed in otherwise expression-incompetent human cells (e.g., CD40+ cells), as suggested in the Kipps application. Nothing in the references points one to select a CD154/TNFα chimera lacking a metalloproteinase site in particular, nor do the references offer a reasonable basis upon which to expect that cleavage from such a chimera would be abrogated to the same or greater degree than demonstrated by Mueller, et al. for the TNF molecule they tested. Even in view of the Kipps application's disclosure, one could not have predicted, *a priori*, the best combination of TNF family member segments to fuse to the domain IV of TNF to create a stabilized molecule.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 4/30, 2007

Signed at: Pittsburgh, Pennsylvania

Dr. Kenneth A. Foon